well says, they would tend to discourage efforts in the way of treatment, for which no such good results can be claimed. In fact, if they prove anything, they show that treatment has no power to diminish the duration of the disease or its mortality. This is, it is scarcely necessary to say, not Dr. Flint's opinion, for among his conclusions we find that life is prolonged by hygienic measures and by the use of medicines, and especially by that of cod-liver oil. The class of cases in which no treatment is employed, is that in which there are no distressing symptoms, such as fever, cough, pain, and the like, for which the sufferer generally seeks relief at the hands of the physician. In other words, there is, in these cases, a remarkable tolerance of the disease, which consequently tends to run a very slow course.

Among the various hygienic measures which have been recommended in phthisis, the author thinks very highly of sea-voyages and of a change of climate, the latter partly in consequence of the change of habits which is often brought about by it. He recommends, where pecuniary or other reasons prevent the patient seeking relief in travel, that he should abandon, if possible, a sedentary and in-door for an active pursuit in the open air, having known the disease to be often arrested under these circumstances. Cod-liver oil he has found to have, as we have already said, the effect of slightly prolonging life. He does not consider the evidence in favour of the curative properties of the hypophosphites sufficiently convincing to recommend their employment. He does not object to the use of alcohol in moderate doses, but says it should never be pushed far enough to produce its exciting effects. There is very little said in the volume about other medicines; but the author takes occasion to say that a bad effect of the theory of the inflammatory origin of phthisis, may possibly be that those who have adopted it may be disposed to employ antiphlogistic remedies in its treatment. At a time when even sthenic inflammations are treated by restoratives, the danger from this source does not seem very great.

The concluding chapter in the book is devoted to the discussion of the physical signs and diagnosis of phthisis. To say that Dr. Flint has added very materially to the knowledge of the signs by which diseases of the lungs may be recognized, is to say what every reader of this journal is perfectly familiar with. J. H. H.

ART. XXV.—*Experimental Investigation of the Action of Medicines.* By T. LAUDER BRUNTON, M.D., Sc.D., F.R.S., M.R.C.P., Assistant Physician and Lecturer on Materia Medica and Therapeutics at St. Bartholomew's Hospital. Part I. Circulation. 8vo. pp. 87, iv. London: J. & A. Churchill, 1875.

THIS neatly printed volume of eighty-seven pages, with a short appendix, is a reprint from the *British Medical Journal.* The author is already favourably known as an earnest, skilful worker in the field of experimental physiology. He has given us in the present very readable and suggestive work, the results of a careful and critical induction from experiments scientifically performed upon the lower animals for the purpose of testing the action of various remedies.

To the clinician, as well as the physiologist, the *modus operandi* of medicines must ever be a subject of earnest inquiry. Nothing more thoroughly distinguishes the empiric, or the mere routinist, from the really educated physician than the manner in which he prescribes his remedies. The hap-hazard guesswork of the one contrasts forcibly with the calm, logical assurance of the other. Teachers of therapeutics have widely differed in their views as to the proper manner of presenting this subject to their readers or hearers. Some, regarding drugs as having reference exclusively to the sick, consider them only from the standpoint of disease; and they accordingly study their action merely in connection with the morbid states of the body. But this is evidently a narrow and distorted view, inasmuch as different diseases must differently modify the action of the same drug. Opium and mercury may be cited as illustrations that will readily occur to the reader. Others, more philosophically, propose to establish the normal action of drugs on the human economy by ascertaining, first, how they will affect the healthy organism: this being verified by repeated experiments, it will be comparatively easy to study the interferences caused by this or that particular disease. Undoubtedly, the latter is the true method of studying the department of therapeutics. Here we have a solid, substantial basis to build upon; and it is to this method that the researches of our most distinguished modern investigators have reference. Our author very aptly compares it to the practice of the rifleman who, "before he stands sentry in the dark, must learn to shoot by daylight, when he can note the effect of each alteration in the position of his rifle on the course of the bullet."

Dr. Brunton most wisely regards a knowledge of the *pathology* of the disease as the corner-stone of rational therapeutics. In order to administer the right medicine, the physician must first know what is the exact morbid change, and where is its seat. This is a truism, but of what vast significance is it! He who has mastered this point may in truth be considered as master of the situation.

> "We must trace every symptom which we see back to its unseen source: every flush on the cheek, every quickening of the pulse, back to the vaso-motor or cardiac nerves which have allowed the capillaries to become dilated, and thus produce the redness, or have permitted the heart to beat more rapidly than its wont. We must then inquire what has produced this alteration in the nervous system, and so on, till at last we have discovered, if possible, the hidden cause of the mischief."

We fully accord with the author in his definition of *pathology:*

> "When I speak of the pathology of a disease, I do not mean those obvious alterations in the structure of an organ which we meet with in *post-mortem* examinations, but the so-called functional changes which precede and are the cause of both them and the symptoms."

He then cites, as examples, abscess of the liver and fatty degeneration of the kidney; in neither case is the obvious structural alteration the *real* disease; but this latter is "the alteration in the nervous and vascular systems, and in the nutrition of tissues, which we call the inflammatory process, and which produced the abscess and degeneration."

We have all probably been too much in the habit of drawing the line between what we term *organic* and *functional* disorders; whereas the truth is gradually becoming more accepted by pathologists and therapeutists—thanks to the microscopist—that every deviation of function involves necessarily a change in structure; so that all the so-called "functional" diseases are to be treated as resulting from alteration of some tissue or fluid.

Under the head of *Pharmacology*, Dr. Brunton gives some valuable practical hints. Here, the first object is to ascertain on what particular structure the remedy acts. This cannot be effected by the hap-hazard exhibition of the said remedy to a man, sick or well. "By so doing we may, to be sure, find out what general symptoms it produces; and possibly from these, guess at the structure effected; but in order to convert our hypothesis into certainty, we must apply it to these structures and organs, and to these alone, and see whether the general result is the same; or we may prevent it from reaching them, while it is applied to all other parts of the body, and observe whether the effect is absent." Of course, as these experiments cannot be made on man, recourse must be had to the lower animals, —and *necessitas non habet legem.*

Treating of *Conditions of Health and Disease*, the author brings out some valuable old truths, which, however, lie at the very foundation of our science. As health consists in the due proportion between assimilation and decompsition and the removal of the waste products, it is vitally important that the "conditions of life" should be duly supported. The chief of these are oxygen (to supply combustion and evolve force), and a due amount of nutriment. Studying these "conditions" under the simplest forms of life —a single cell or a mass of protoplasm—we see at once the consequences of their withdrawal: "If oxygen be withheld, or the products of the waste be not removed, the combustion will cease, and the cell will die. If nutriment be withheld, the cell will begin to burn away." If the supply of oxygen and nutriment be insufficient, and the effete materials be only partially removed, "the cell may adapt itself to the altered circumstances," but in a deranged condition, and *disease* is the result.

Effect of Drugs.—If, as just shown, the nutrition of a cell—and consequently of an organ or system—may be altered by a faulty supply of oxygen and nutriment, it may equally be modified by the addition of various drugs to the nutrient fluid; thus, "a weak solution of alkali may increase or diminish the rapidity of the changes which it undergoes, by hastening the removal of waste products if they be acid, or retarding it if they be alkaline; while a weak acid will have an opposite effect." Other substances may arrest the changes altogether "by forming a firm compound with the substance of the cell;" while others again would seem to produce merely a temporary impression on the organ, but passing out and leaving it in its primitive condition. But even these temporary changes resulting from the presence of a drug, and which are usually spoken of as functional, the author is disposed to ascribe to a real, though not always demonstrable, "chemical or physical change."

The *Direct and Indirect Action of Drugs* is well illustrated by the author by the instance of curare. This substance, when given to an animal, paralyzes the peripheral ends of motor nerves (its *direct* action); but it may happen that the respiratory nerves may become paralyzed before the motor, in which case respiration ceases, the blood is not aërated, and convulsions occur as the result of the action of the retained carbonic acid on the nerve-centres; the asphyxia here is produced by the *indirect* action of the curare.

On the subject of *Dose*, we find some very suggestive observations. In the first place, we should distinguish between the ordinary dose that is administered by the stomach or other avenue, and the *actual dose*—"that actually existing in the blood at any given time." It is the latter alone which is active; the balance is, for the time being, totally inoperative (except in the case of purely local remedies, as the mineral acids). We suspect that this truth is often lost sight of by the practitioner; it should certainly act as a check to immoderate dosing. Under this head we should remember the relation subsisting between the amount of the drug and the weight of the subject, "since an amount which is a small dose for one person is a very large one for another." "The dose of the drug must therefore be regulated by the weight of the patient; and thus women, being lighter, require a smaller amount than men, and children less than adults." This rule should specially be observed in experiments upon animals—to proportion the size of the dose to the weight of the animal.

The subject of the *absorption* and *elimination* of medicines is one of profound interest and importance to the therapeutist, but it can only be alluded to here very cursorily. The reason of the exceedingly rapid effect produced by injecting the substance directly into the blood, is because the whole of it mixes with the blood, and becomes active immediately; and this effect continues until excretion is established; whereas by the other routes of entrance (especially by the stomach) the process of absorption being comparatively slow, that of excretion commences immediately, and goes on with the former, "and thus part of the drug is passing out of the blood, while another part is being taken in." Moreover, the "actual dose" always bears a distinct proportion between the amount absorbed and the amount excreted; it is, in fact, "the difference between that absorbed and that excreted in a given time; and absorption may be so slow, or excretion so quick, that there is never a sufficient amount of the substance in the blood to produce any effect." On the other hand, if the absorption be rapid, and the excretion slow, the maximum effect of the drug will be obtained. This (in passing) affords us a valuable hint in the treatment of cases of poisoning, viz., *to prevent absorption and promote elimination*. The main channel for excretion is, of course, the kidney; and hence the practical importance of inspecting the urine in all cases of suspected poisoning, especially mineral. The other routes of excretion, as is well known, are the lungs, skin, salivary glands, and liver.

As the rapidity of absorption varies materially with the tissue to which the medicine is applied, the dose must be correspondingly varied. According to the author, "absorption is quickest from a serous membrane; then from intercellular tissue, and lastly from mucous membrane." This is undoubtedly true for liquids; but, for gases and vapours, the absorption is most rapid from the respiratory *mucous* surface, as is familiarly witnessed in the rapid anæsthesia produced by the inhalation of ether, chloroform, etc. The relative rapidity of the absorption and elimination of a drug will satisfactorily explain what is termed the *cumulative action* of medicines. Remembering that it is only the "actual dose"—that which is actually circulating in the blood at a given time—that produces any effect, it is easily understood that if repeated doses of the same substance be given before the preceding one has been completely excreted, the amount present must gradually increase, and, of course, its action be intensified. On the other hand, the very rapid elimination of some substances by the kidneys, lungs and skin, may prevent this accumulation in the blood, and occasion a proportionately transient effect, as in the case of alcohol and curare. Hermann's experiment with the latter drug demonstrated that the cause of its inertness when taken into the stomach was owing to the rapidity of its excretion by the kidneys; for "by tying the ureters (whereby this elimination was prevented), the animal became paralyzed as surely as if the poison had been introduced at once into the veins, though not so quickly."

The *Effects of Habit, Climate, Fasting, and Form of Administration*, are very briefly discussed by our author, although with sufficient precision for his present purpose. He ascribes the differences in the action of medicines resulting from *constitution* and *idiosyncrasy* as being really due "to differences in absorption and excretion, or to the different relative development of other parts, especially parts of the nervous system."

The important question is next discussed, "How far conclusions as to the action of medicines on man may be drawn from those which they exert on the lower animals." He evidently adopts the affirmative side of the proposition, and adduces in its support the action of curare in paralyzing the ends of motor nerves as being identical "in the Indian who accidentally wounds himself with his poisoned arrow, in the game which he shoots, or in the frog on which we experiment. Motor nerves, the structures on which curare acts, are alike present in all, and in all are its results the same." He admits that the action will be alike only "when the organs and structures on which a drug acts are similar in man and the lower animals; and that variations will be observed just in proportion to the difference between his structure and theirs;" and inasmuch as these differences of structure are not always susceptible of demonstration, "we ought to test our conclusions as to the action of remedies by giving them to a healthy man, and observing whether their effects are such as we have been led, from our experiments on animals, to expect."

Finally, under this head, the relationship between the *Chemical Constitution and Physiological Action* of medicines is briefly discussed. If a change in the constitution of the living cell may change the operation of a medicine, there can be no reason to doubt that a change in the constitution of the drug itself must produce a variation in its effects upon the system.

Chapter II. introduces us into the field of experiment. The leading idea of the author is "to *localize* the action" of the drug employed—"to be able to say with certainty, This is the organ on which this medicine acts, and such is the action which it exerts upon it." One of the methods of effecting this is by experimenting on a highly organized animal resembling man in its general structure, "allowing the medicine to act now on one, and now on another part of the body, but never on all at once, till we find out those parts for which it has a particular affinity." A timely caution is here interposed, not to confound the observations of the experimenter with his conclusions; since, while the former may be quite correct, the latter may be erroneous. Of course, to be of any real value, each experiment requires frequent repetition. Another practical caution to the experimenter is, that "he should note down the results at the time, and not trust afterwards to his memory" to recall them.

The methods are given for studying the action of drugs on Protoplasm, Vibriones, and Bacteria, on Fungi, on Fermentation and Putrefaction, on White Blood-corpuscles, and on Inflammation; and the results of the different reagents are noted, together with some therapeutic deductions.

In the *administration of drugs* to animals, among the different methods employed, the preference is, we think, very properly given to the subcutaneous injection, as being the most certain in its results, and also easy of practice.

Under the head of *Interpretation of Results*, we meet with such fair logical deductions as the following: "If we find that voluntary motion is increased or lessened by the experiment, we may naturally conclude that the activity of the cerebrum is increased or diminished." "Unsteady movements, paralysis, or convulsions, impaired reflex action on pinching, or stoppage of respiration before the heart, point to the spinal cord, to the nerves, or to the muscles; while quick or slow, strong or weak pulse, or stoppage of the heart before respiration, point to the vaso-motor system, or cardiac nerves; increased or diminished secretion, to secreting nerves, etc." In cases where the drug used is poisonous, it is always proper to ascertain its *minimum fatal* dose; and also calculate this dose for every pound weight of the animal.

The rest of this chapter is occupied with a description of the various "modes of securing animals" for experimentation, with diagrams of the necessary apparatus required—such as Czermak's rabbit-holder, Bernard's and Brunton's holders for dogs; also the modes of making glass canulæ and tubes for a variety of uses in such experiments. As regards the best method of narcotizing animals, before experimenting upon them (which operation considerations of humanity should always, if possible, lead us to practise), Dr. Brunton recommends opium and chloral; and curare, when it is desired to render the animal perfectly motionless. The difference in the action of the various narcotics on animals is discussed and illustrated, and their proper dose and mode of administration noticed.

We have next described the proper method of injecting fluids into the bloodvessels; the mode of division and irritation of nerves; the proper method of performing artificial respiration on animals, and of introducing gases and vapours into their lungs.

Chapter III. describes *Artificial Circulation of Blood, warm and cold; and Investigations on Blood-pressure.* Under the former head our author notices Prof. Ludwig's curious experiment of injecting *cold* blood into the vessels of the muscle of a warm-blooded animal, immediately after it had been removed from the body; the muscle will retain its irritability for a long time, just like that of the cold-blooded frog.

The *Influence of Nerves on Blood-pressure* forms an interesting and instructive portion of this chapter. Several distinct parts of the nervous system are concerned in the circulation, as follows: 1. "The *cardiac ganglia*, which lie in the walls of the heart, and are, in all probability, the cause of its rhythmical action." 2. "*Inhibitory nerves*, which render action slow, and, if irritated very strongly, may stop its beating altogether." "A drug may irritate these nerves, and render the heart's action slow in various ways. . . . . Drugs may also paralyze the inhibitory fibres, and thus quicken the heart." 3. "*Quickening nerves*, belonging to the sympathetic system." These also may be irritated by drugs, both directly and indirectly. 4. "*Vaso-motor nerves*, which cause the small arteries, and probably also the capillaries, to contract." These belong to the sympathetic system. "The most important of them are the splanchnics, which produce contraction of the intestinal vessels." . . . . "The centre of the whole vaso-motor system seems to be the medulla oblongata; and it is generally in constant action, keeping up a certain amount of contraction or tone in these vessels." This contraction may be increased by direct stimulation of the nerve-centre, and by reflex irritation through the cervical sympathetic, the vagus, and sensory nerves. 5. *Vaso-inhibitory nerves.* "Irritation of these nerves is conducted to the vaso-motor centres, and acts on them in such a way as to cause a reflex dilatation of the small vessels either through the whole body or in one particular part of it."

As the action of drugs upon the circulation is the main object of the author's investigation in the present essay, he naturally devotes the bulk of his remarks to *experimental examination of blood-pressure.* He describes in detail what he conceives to be the best form of the manometer, one form of which, termed *kymographion*, is a self-registering instrument, complex in its construction, and very different in appearance from the original simple contrivance of Hales, and the bent-tube mercurial hæmadynamometer of Poiseuille.

Chapter IV. is replete with most interesting and suggestive experiments, made to determine the true means by which drugs affect the heart and vessels. First of all, a careful comparison is made, by means of the kymographion, of the effects of the drug in question on different animals. Then, by induction from most careful experiments, important conclusions are arrived at in relation to the real structures affected by the drug, as, *e. g.*, the vagus, the sympathetic, the cardiac, and other ganglia; and for all these structures the very important question is settled, whether the action of the medicine is direct or reflex.

The unquestionable physiological antagonism of atropia and physostigma within certain limits, as previously shown by Dr. Fraser, is alluded to by the author for the purpose of indicating a valuable rule in therapeutics, viz., in the treatment of such diseases as have their origin in morbid matter introduced into the system, and consequently, in cases of poisoning, we are not always to wait to eliminate the noxious agent from the organism (though, of course, this is highly important), but we should seek to neutralize and render it innocuous even while still present in the system.

Various other topics kindred to those above mentioned are discussed by the author in this chapter, to which we cannot, at present, bestow even a passing attention. From what we have already indicated, our readers will readily admit that there is much in the present volume that will amply repay an attentive perusal; and to such as wish to cultivate this most interesting but difficult branch of physiological and therapeutical research, we confidently recommend Dr. Brunton's book for careful study. We shall look with much pleasure for the appearance of the succeeding portions of his work. J. J. R.